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Total Synthesis of Caprazamycin A: Practical and Scalable Synthesis of *syn*- β -Hydroxyamino Acids and Introduction of a Fatty Acid Side Chain to 1,4-Diazepanone

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Supporting Information Placeholder

ABSTRACT: The first total synthesis of caprazamycin A (**1**), a representative liponucleoside antibiotic, is described. Diastereoselective aldol reactions of aldehydes **12** and **25–27**, derived from uridine, with diethyl isocyanomalonate **13** and phenylcarbamate **21** were investigated using thiourea catalysts **14** or bases to synthesize *syn*- β -hydroxyamino acid derivatives. The 1,4-diazepanone core of **1** was constructed using a Mitsunobu reaction, and the fatty acid side chain was introduced using a stepwise sequence based on model studies. Notably, global deprotection was realized under using palladium black and formic acid without hydrogenating the olefin in the uridine unit.

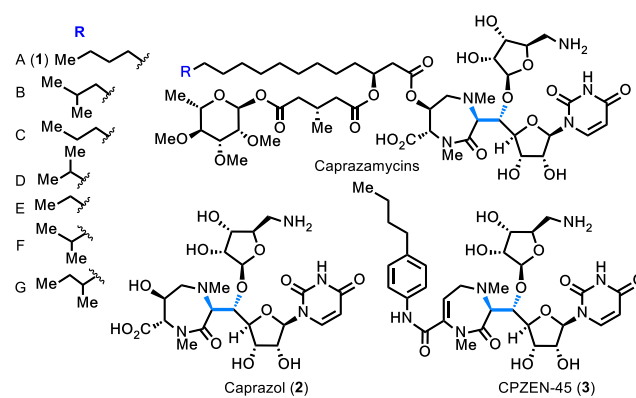


Figure 1. Caprazamycins, caprazol, and CPZEN-45.

Introduction

Liponucleoside antibiotics are a class of natural products with structures comprising uridine attached to amino acids, namely 5'-C-glycyluridine, an aminoribose, and a fatty acid side chain. Examples include caprazamycins,⁽¹⁾ liposidomycins,⁽²⁾ muraymycins,⁽³⁾ A-90289,⁽⁴⁾ and sphaerimicins⁽⁵⁾ (Figures 1 and 2). Several liponucleoside antibiotics inhibit bacterial translocase *MraY*, which is a peptide glycan enzyme.⁽⁶⁾ In the biosynthetic pathway, *MraY* is located upstream of the enzyme targeted by β -lactam antibiotics and glycopeptide antibiotics (such as vancomycin). Therefore, novel antibiotics targeting *MraY* are expected to have a broad antimicrobial activity spectrum, including against multi-drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA).

Caprazamycins were isolated from *Streptomyces* sp. MK730-62F2 by Igarashi and coworkers in 2003 (Figure 1).⁽¹⁾ Structurally, these molecules possess a 1,4-diazepanone, which is a seven membered ring containing two nitrogen atoms, retaining the common motif of several liponucleoside antibiotics. The biosynthesis of caprazamycins was proposed through *in vivo* and *in silico* analysis of the biosynthetic gene cluster.⁽⁷⁾ Recently, an enzyme catalyst that promotes an aldol-type condensation with glycine and uridine-5'-aldehyde to construct 5'-C-glycyluridine was identified.⁽⁸⁾ Caprazamycins show

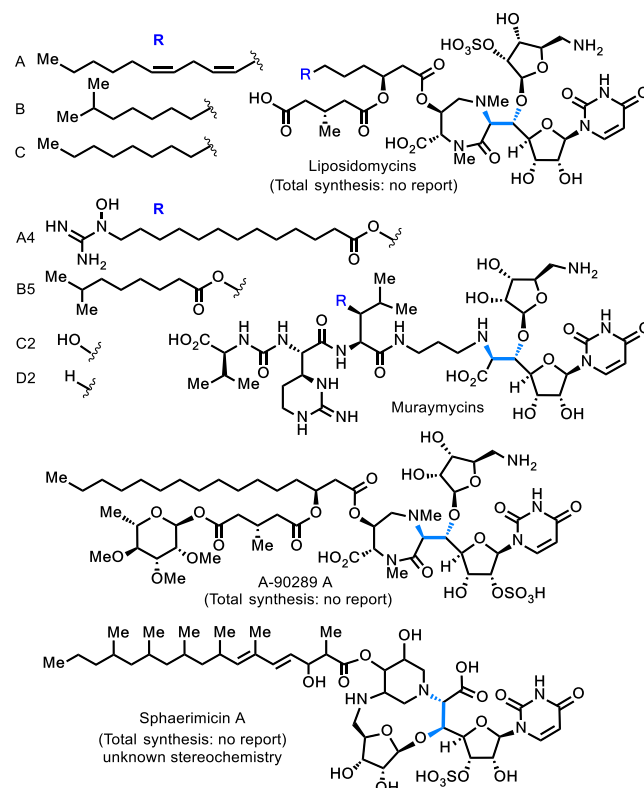
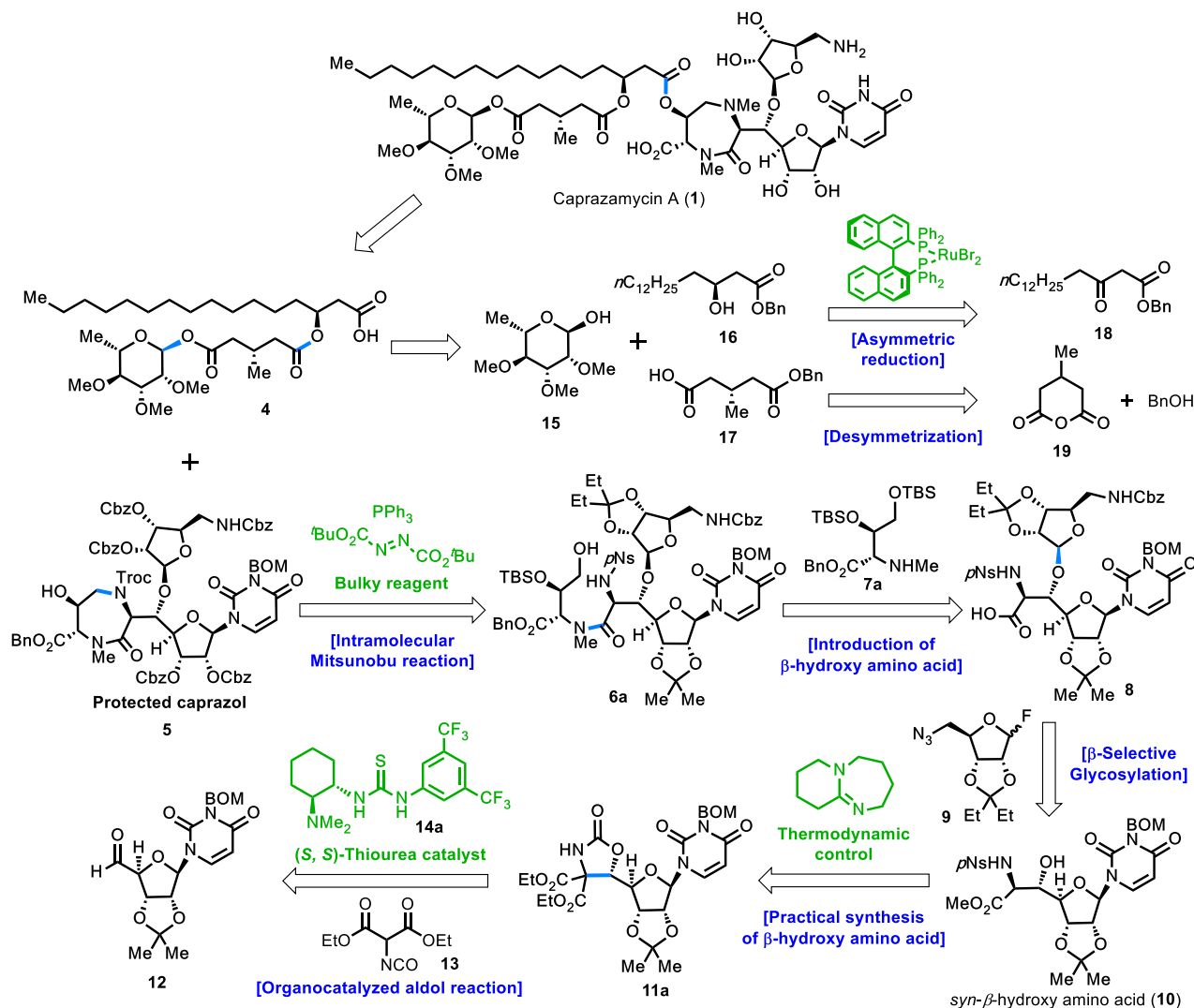


Figure 2. Structures of representative liponucleoside antibiotics.



Scheme 1. Retrosynthetic analysis of caprazamycin A (1)

antibacterial activity against *Mycobacterium tuberculosis*, including the multi-drug resistant strain (MDR-TB), by inhibiting MraY as mentioned above.⁽¹⁾ Through caprazamycin derivatization, Takahashi and coworkers developed CPZEN-45, which exhibits more potent antibacterial activity, particularly against extensively drug-resistant tuberculosis (XDR-TB).⁽⁹⁾ As MDR-TB and XDR-TB are resistant to at least four of the core anti-TB drugs, including isoniazid and rifampicin, they present a potential public health problem. Therefore, caprazamycins and CPZEN-45 are receiving attention as seed compounds for future effective antibiotic drugs. Owing to its important biological activity and complex structure, we expected a total synthesis of caprazamycins to provide not only a synthetic sample and route for synthetic analogs, but also an opportunity to develop new synthetic strategies.

Synthetic plan

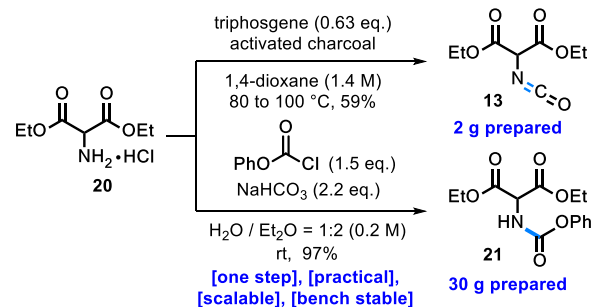
When we began investigating the synthesis of liponucleoside antibiotics, the total synthesis of caprazamycins and liposidomycins had yet to be reported, although various synthetic studies towards liponucleoside antibiotics had been published.^(10–14) In 2008, Ichikawa, Matsuda, and coworkers achieved the first total synthesis of caprazol (2), which is a core structure in caprazamycins.^(6e) In their synthesis, a Sharpless aminohydroxylation and reductive amination were key reactions for constructing the *syn*- β -hydroxyamino acid moiety and 1,4-diazepanone core, respectively. After this landmark report, Shibasaki, Watanabe, and coworkers reported a total synthesis of caprazol (2) in 2013 based on a Cu-catalyzed diastereoselective aldol reaction used to construct the *syn*- β -hydroxyamino acid moiety.^(13c) However, the introduction of a caprazamycin-type fatty acid side chain has not been reported. These preceding studies indicated that the synthesis of liponucleoside antibiotics presented the following challenges: (i) Construction of the *syn*- β -hydroxyamino acid moiety, (ii)

formation of the 1,4-diazepanone core, and (iii) introduction of the fatty acid side chain. To achieve a total synthesis of caprazamycin A (**1**), fatty acid side chain **4** would need to be introduced to caprazol core **5** at the late stage because these substructures were expected to be unstable under acidic and basic conditions due to the presence of β -acyloxyester and acyloxy acetal moieties (Scheme 1). Benzyl (Bn), benzyloxymethyl (BOM), and benzyloxycarbonyl (Cbz) groups were selected as protecting groups for the caprazol core **5** that could be removed under mild conditions. The 1,4-diazepanone motif in **5** would be constructed through a Mitsunobu reaction⁽¹⁵⁾ of alcohol **6a**, itself accessed from *syn*- β -hydroxyamino acid derivative **10** through β -selective glycosylation with glycosyl fluoride **9**^(12e) and coupling with secondary amine **7a**. To construct the *syn*- β -hydroxyamino acid moiety, we developed an asymmetric synthesis of trisubstituted oxazolidinones through the thiourea-catalyzed aldol reaction of 2-isocyanatomalonate diester **13**.^(16,17) Extending this method, *syn*- β -hydroxyamino acid derivative **10**, which is a protected 5'-C-glycyluridine, would be synthesized from aldehyde **12** through a diastereoselective aldol reaction with **13** using thiourea catalysts **14**, followed by ring opening of the resultant oxazolidinone **11a** and decarboxylation. In this aldol reaction, the thiourea catalyst must precisely recognize a nucleophilic site (aldehyde) to achieve high stereoselectivity, which is challenging owing to the presence of several functionalities, including ether, imide, and *N,O*-acetal groups. The fatty acid side chain would be synthesized by coupling rhamnose derivative **15**, β -hydroxyester **16**, and carboxylic acid **17** (vide infra). In this report, we describe in full detail the first total synthesis of caprazamycin A, which was achieved by overcoming the three challenges described above.⁽¹⁸⁾

Results and discussion

1. Diastereoselective synthesis of *syn*- β -hydroxyamino acid moiety

To investigate the diastereoselective aldol reaction, diethyl isocyanomalonate **13** was prepared from diethylaminomalonate hydrochloride **20** using triphosgene following a literature procedure (Scheme 2).⁽¹⁹⁾ As diethyl isocyanomalonate **13** readily polymerizes in the presence of trace amounts of water, it was used immediately after preparation. When water was removed by Kugelrohr distillation, the distilled diethyl isocyanomalonate **13** could be stored for several weeks. Phenyl carbamate **21**, which is much more stable than **13**, was also prepared in 97% yield by treating **20** with phenyl chloroformate and sodium bicarbonate under Schotten–Baumann conditions.



Scheme 2. Preparation of isocyanate **13** and phenylcarbamate **21**.

Initially, the diastereoselectivity of the aldol reaction of aldehyde **12**, prepared from a known protected uridine by IBX oxidation,⁽²⁰⁾ with diethyl isocyanomalonate **13** or phenylcarbamate **21** was examined in the absence of thiourea catalyst **14a** (Table 1). While the aldol reaction with isocyanate **13** using 1,8-diazabicyclo(5.4.0)-7-undecene (DBU) as base (10 mol%) afforded oxazolidinones **11a** and **11b** in 42% yield, no selectivity was observed (entry 1). Using Et₃N or K₂CO₃ as base did not improve the selectivity (entries 2 and 3). Under these conditions, a small amount of byproduct **22** was obtained through the reaction of products **11a** and **11b** with diethyl isocyanomalonate **13**. Therefore, less-reactive phenylcarbamate **21** was employed as a nucleophile. Treatment of aldehyde **12** with phenylcarbamate **21** (1.0 equiv.) and DBU (1.0 equiv.) in THF at room temperature gave a 1:2.2 mixture of desired oxazolidinone **11a** and undesired isomer **11b** in 59% yield through phenylcarbamate addition and PhOH elimination (entry 4).

To control the selectivity through chelation, several additives were tested.^(11v,21,22) Adding ZnCl₂ did not affect the selectivity (entry 5). The aldol reaction with LiBr (1.0 equiv.) resulted in a 56% yield with a 1:1.5 dr (entry 6). In this reaction, a small amount of **23** was obtained from elimination of the uracil moiety. To reverse this diastereoselectivity, we applied the same conditions using (*S,S*)-thiourea catalyst **14a**, which was developed for the asymmetric aldol reaction of aldehydes.⁽¹⁶⁾ The reaction of **12** with diethyl isocyanomalonate **13** in the presence of **14a** (10 mol%) proceeded smoothly, affording desired oxazolidinone **11a** as the major product (64%, 3.1:1 dr, entry 7). It was significant that the selectivity of this aldol reaction could be reversed using an organocatalyst. Both the yield and diastereoselectivity were improved (77%, 6.5:1 dr) using (*S,S*)-thiourea catalyst **14b** (10 mol%) bearing a bulky tertiary amine moiety (entry 8). The amount of catalyst **14b** could be reduced to 7 mol%, although this slightly decreased the diastereoselectivity. Interestingly, the formation of byproduct **22** was suppressed by reducing the amount of catalyst **14b**. When the amount of catalyst was reduced to 5 mol%, the reaction proceeded slowly to give oxazolidinones **11a** and **11b** in 68% yield, but with 4.2:1 dr, and a small amount of starting

Table 1. Diastereoselective aldol reaction of aldehyde **12** with thiourea catalysts **14**.

12 + **cat. 14a or 14b or base** + **R' 13 or 21 (1.0 equiv.)** → **11a (desired)** + **11b (undesired)**

[Organocatalyzed aldol reaction]

entry	nucleophile (R')	cat. 14a or 14b or base	solvent	results (11a : 11b)	byproduct
1	13 (R' = NCO)	DBU (10 mol%)	PhMe	42% (dr = 1:1)	22 : 27%
2	13 (R' = NCO)	Et ₃ N (10 mol%)	PhMe	50% (dr = 1:1.8)	22 : 10%
3	13 (R' = NCO)	K ₂ CO ₃ (10 mol%)	PhMe	60% (dr = 1.3:1)	22 : 13%
4	21 (R' = NHCO ₂ Ph)	DBU (100 mol%)	THF	59% (dr = 1: 2.2)	—
5	21 (R' = NHCO ₂ Ph)	DBU (100 mol%), ZnCl ₂	THF	31% (dr = 1:2.1)	—
6	21 (R' = NHCO ₂ Ph)	DBU (100 mol%), LiBr	THF	56% (dr = 1:1.5)	23 : 3.8%
7	13 (R' = NCO)	(S,S)- 14a (10 mol%)	PhMe	64% (dr = 3.1:1)	22 : 7%
8	13 (R' = NCO)	(S,S)- 14b (10 mol%)	PhMe	77% (dr = 6.5:1)	22 : 9%
9	13 (R' = NCO)	(S,S)- 14b (7 mol%)	PhMe	81% (dr = 5.0:1)	22 : 0%
10	13 (R' = NCO)	(S,S)- 14b (5 mol%)	PhMe	68% (dr = 4.2:1)	— ^{a)}
11	13 (R' = NCO)	(R,R)- 14b (10 mol%)	PhMe	80% (dr > 1:20)	22 : 9.5%

byproduct **22**

byproduct **23**

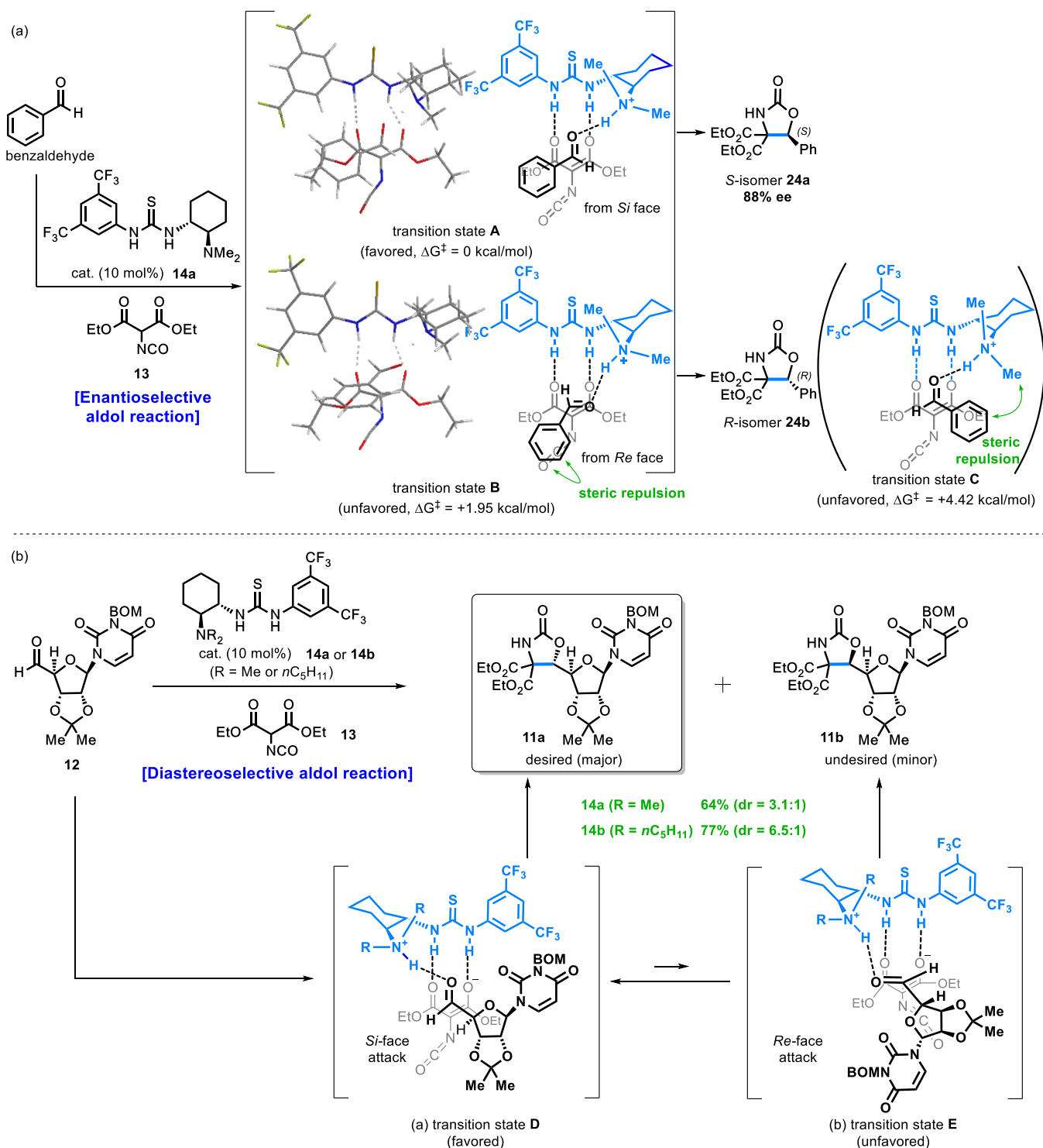
a) 15% of starting material **12** was recovered.

material **12** was recovered (entry 10). Interestingly, the aldol reaction using (*R,R*)-thiourea catalyst **14b** (10 mol%) gave undesired isomer **11b** in 80% yield in a highly diastereoselective manner (>1:20 dr) (entry 11). These results indicated that the aldol reaction of aldehyde **12** with (*R,R*)-thiourea catalyst **14b** was a matched pair that afforded undesired isomer **11b**.

To explain this diastereoselectivity, a computational model study of this thiourea-catalyzed aldol reaction using benzaldehyde was conducted based on a DFT calculation (Scheme 3a, B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level).⁽²³⁾ The calculation suggested that transition state **A** was more favorable than transition state **B**, in which there was steric repulsion between the phenyl and isocyanate groups. Transition state **C**, which is another possible transition state towards undesired isomer **24b**, was not more favorable than **B**, because **C** would be destabilized by steric repulsion between the tertiary amine and uracil moieties. Consequently, isocyanomalonate **13** would approach from the *Si* face of benzaldehyde to give *S*-isomer **24a**. Indeed, this reaction gave *S*-isomer **24a** in 87% yield with 88% ee.⁽¹⁶⁾ Considering these results, the stereoselectivity of the reaction of aldehyde **12** with **13** using thiourea catalyst **14** was rationalized using the following reaction mechanism (Scheme 3b). Initially, thiourea catalyst **14** recognizes the two carbonyl groups of isocyanomalonate **13**

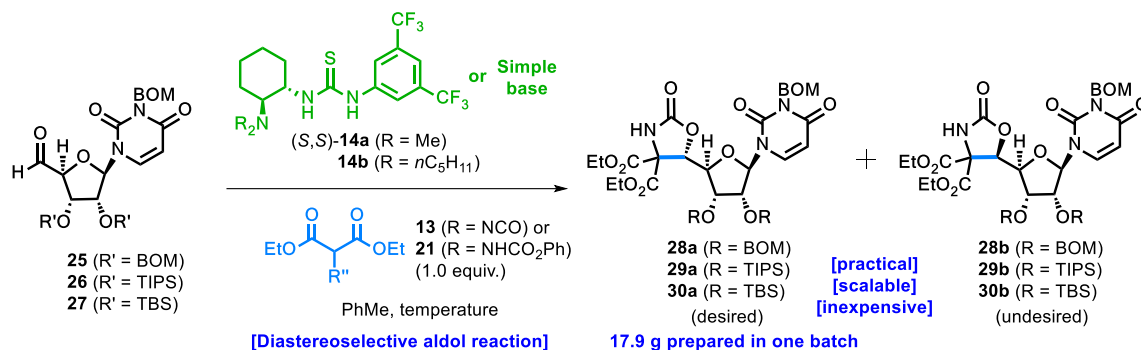
through hydrogen bonding. The protonated tertiary amine moiety of thiourea catalyst **14** interacts with the carbonyl group of aldehyde **12** through hydrogen bonding to afford transition state **D** rather than transition state **E**. Subsequent cyclization of the resultant alcohol with isocyanate gave desired oxazolidinone **11a** as the main product.

We also investigated the aldol reaction of the related aldehydes **25–27**,^(24–26) in which two hydroxyl groups were protected as benzyloxymethyl (BOM), triisopropylsilyl (TIPS), and *t*-butyldimethylsilyl (TBS) ethers instead of isopropylidene acetal (Table 2). When aldehyde **25** was treated with isocyanomalonate **13** and (*S,S*)-thiourea **14a** in toluene at 0 °C to room temperature, the reaction proceeded to give desired product **28a** in 55% yield with >9:1 dr (entry 1). In contrast, when (*R,R*)-thiourea catalyst **14b** was used in an attempt to reverse the diastereoselectivity, diastereomer **28b** was obtained as a minor product (2:1 dr, entry 2). As such diastereoselectivity was not obtained using aldehyde **12** bearing an isopropylidene acetal, it was assumed that this selectivity was derived from the bulkiness of the hydroxy protecting groups and/or the conformation of aldehyde **25**.⁽²⁷⁾ Therefore, the reaction was also performed without chiral thiourea catalyst. When potassium carbonate was used as a basic catalyst, the reaction proceeded with high diastereoselectivity (entry 3).

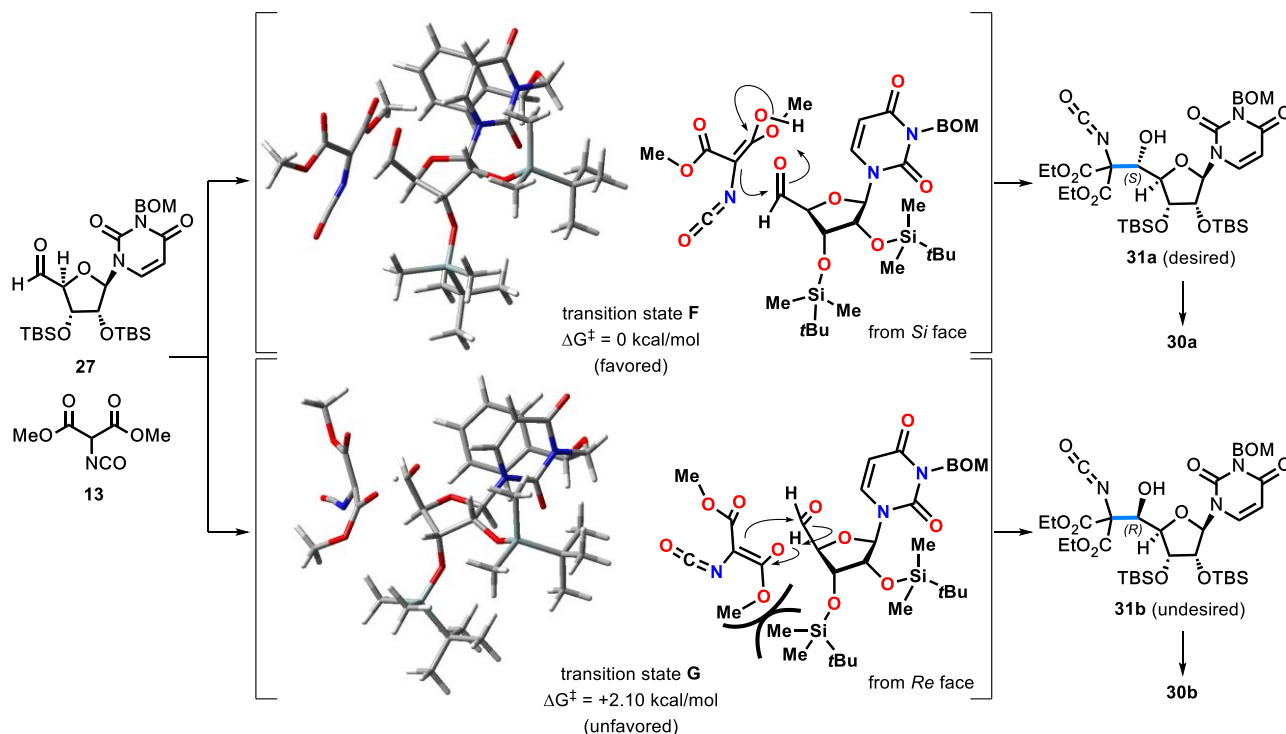


Scheme 3. (a) Computational study of thiourea-catalyzed aldol reaction using benzaldehyde and catalyst **14a**, based on B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) (in a vacuum) using Gaussian 09; (b) rationalization of diastereoselectivity of thiourea-catalyzed aldol reaction of aldehyde **12**

Table 2. Diastereoselective aldol reaction of aldehydes **25–27** with diethyl isocyanomalonate **13** and phenylcarbonate **21**.



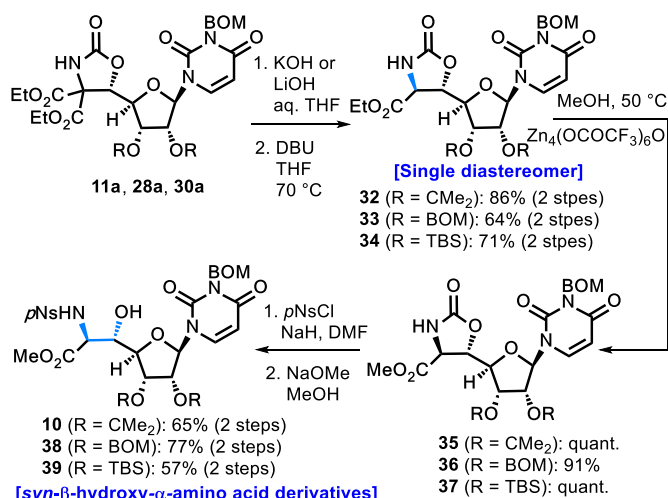
entry	aldehyde (R')	nucleophile (R'')	cat. 14a or 14b or base	temperature	results (a:b)
1	25 ($R' = \text{BOM}$)	13 ($R'' = \text{NCO}$)	(S,S) - 14a (60 mol%)	0 °C to rt	28 : 55% (dr = 9:1)
2	25 ($R' = \text{BOM}$)	13 ($R'' = \text{NCO}$)	(R,R) - 14b (60 mol%)	0 °C to rt	28 : 46% (dr = 2:1)
3	25 ($R' = \text{BOM}$)	13 ($R'' = \text{NCO}$)	K_2CO_3 (60 mol%)	0 °C to rt	28 : 68% (dr = 9:1)
4	26 ($R' = \text{TIPS}$)	13 ($R'' = \text{NCO}$)	K_2CO_3 (10 mol%)	0 °C	29 : 60% (dr = 4.6:1)
5	26 ($R' = \text{TIPS}$)	13 ($R'' = \text{NCO}$)	Et_3N (10 mol%)	0 °C	29 : 53% (dr = 7:1)
6	26 ($R' = \text{TIPS}$)	13 ($R'' = \text{NCO}$)	DIPEA (10 mol%)	0 °C	29 : 71% (dr = 13:1)
7	26 ($R' = \text{TIPS}$)	21 ($R'' = \text{NHCO}_2\text{Ph}$)	K_2CO_3 (100 mol%)	0 °C to rt	29 : 62% (dr = 13:1)
8	27 ($R' = \text{TBS}$)	21 ($R'' = \text{NHCO}_2\text{Ph}$)	K_2CO_3 (100 mol%)	0 °C	30 : 84% (dr > 20:1) (17.9 g scale)



Scheme 4. Computational study of diastereoselective aldol reaction of aldehyde **27** with isocyanate **13**, based on B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) (in a vacuum) using Gaussian 09.

The reaction of aldehyde **26**, bearing TIPS groups, with isocyanomalonate **13** gave desired oxazolidinone **29a** as the major product with 4.6:1 dr. The selectivity was improved by using a tertiary amine, with diisopropylethylamine (DIPEA) proving particularly effective (entries 5 and 6). Furthermore, we attempted reacting **26** with phenylcarbamate **21**, which was easier to handle than isocyanomalonate **13**. Although 1 equiv. of potassium carbonate was required, this reaction proceeded smoothly to give desired oxazolidinone **29a** in 62% yield with 13:1 dr (entry 7). These conditions using **21** could be applied to a large-scale synthesis from aldehyde **27** bearing a TBS group (17-g scale), which could be readily prepared from uridine. The desired oxazolidinone **30a** was obtained in 84% yield with excellent selectivity (entry 8). To explain this diastereoselectivity, we estimated an activation energy for the reaction of aldehyde **27** with isocyanate **13** using DFT calculation at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level (Scheme 4).⁽²³⁾ The results indicated that the activation energy for transition state **F**, which affords desired adduct **31a**, was 2.10 kcal/mol lower than that of transition state **G**, which affords undesired adduct **31b**. In transition state **G**, there is steric repulsion between an ester group in **13** and a silyl group in **27**, which would make transition state **F** preferable. Resulting adducts **31a** and **31b** would immediately cyclize to give oxazolidinones **30a** and **30b**, respectively. Therefore, desired oxazolidinone **30a** would be the major product.

Obtained aldol adducts **11a**, **28a**, and **30a** were converted into *syn*- β -hydroxyamino acid derivatives **10**, **38**, and **39** (Scheme 5). Selective monohydrolysis of **11a**, **28a**, and **30a** followed by decarboxylation gave thermodynamically stable *trans*-oxazolidinones **32–34**, respectively. Transesterification of **32–34** using a tetranuclear zinc cluster⁽²⁸⁾ to afford methyl esters **35–37** was essential for concise oxazolidinone ring-opening.



Scheme 5. Synthesis of *syn*- β -hydroxyamino acid derivatives **10**, **38**, and **39**.

After introducing a *p*-nitrobenzenesulfonyl (pNs) group, the oxazolidinone ring was opened by treatment with NaOMe to afford *syn*- β -hydroxyamino acid derivatives **10**, **38**, and **39** in good yields. Protected compounds **10**, **38** and **39** are useful intermediates for the synthesis of liponucleoside antibiotics. Indeed, we achieved the total synthesis of CPZEN-45 (**3**) from intermediate **39** in 2016.^(14a)

2. Introduction of a fatty acid side chain using model 1,4-diazepanone

Although Shibasaki, Watanabe, and coworkers had reported a synthesis of the fatty acid side chain of caprazamycin B,^(13d) the introduction of fatty acid side chain **4** onto a diazepanone ring had not been reported before we began this synthetic study. Presumably, this was due to the fatty acid side chain containing an unstable β -acyloxycarboxylic acid structure, meaning that β -elimination and acyl group rearrangement might occur under basic conditions (Figure 3).

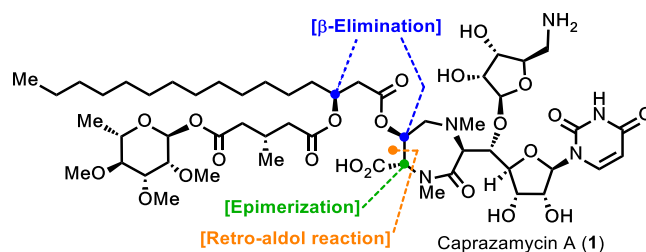
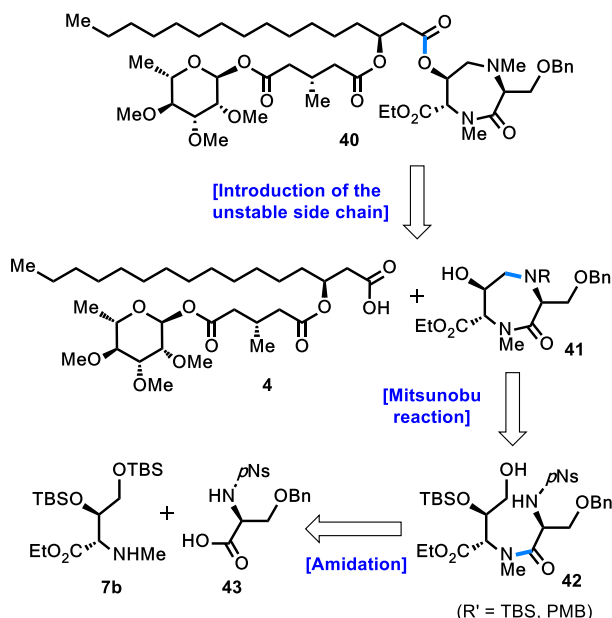


Figure 3. Predictable side-reactions when introducing the fatty-acid side chain of caprazamycin A (**1**)

Furthermore, several side reactions on the diazepanone ring, such as epimerization, β -elimination, and retro-aldol reactions, were expected. Therefore, we initially planned to establish a synthetic route toward model substrate **40** by introducing fatty acid side chain **4** onto diazepanone **41** (Scheme 6).

Simple diazepanone **41** would be synthesized by coupling *anti*- β -hydroxy amino acid derivative **7b** with carboxylic acid **43**, derived from serine,⁽²⁹⁾ followed by an intramolecular Mitsunobu reaction. To prevent undesired side reactions of the β -hydroxy amino acid moiety under Mitsunobu conditions, determining appropriate reaction conditions and protecting groups was important. Fatty acid side chain **4** would be synthesized by coupling known rhamnose derivative **15**⁽³⁰⁾ with carboxylic acid **17**, followed by condensation with β -hydroxy ester **16** (Scheme 1). Intermediates **16** and **17** would be prepared by the Noyori asymmetric reduction of keto ester **18** and the desymmetrization of 3-methyl glutaric anhydride **19**, respectively.^(31,32)

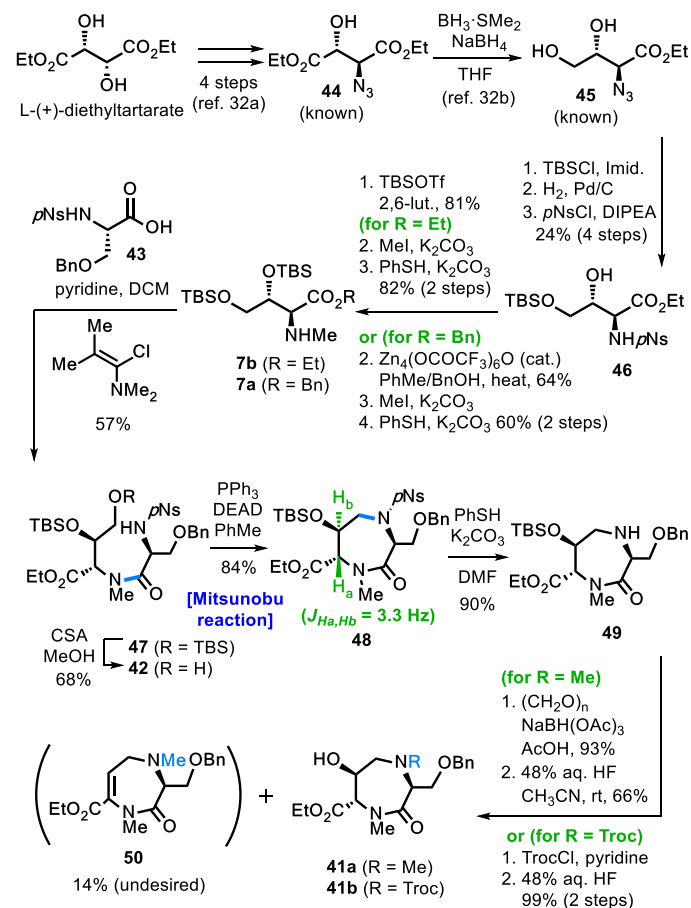


Scheme 6. Planned synthetic route for model diazepanone **41** bearing a fatty acid side chain.

The synthesis started with known diol **45**, prepared from L-(+)-diethyltartrate in a five-step transformation (Scheme 7).⁽³³⁾ Selective silylation of the primary alcohol followed by azide reduction gave an amine that was then protected as the corresponding *p*Ns-amide. Resultant alcohol **46** was converted to *anti*- β -hydroxyamino acid derivative **7b** through silylation of the secondary alcohol, introduction of a methyl group, and removal of the *p*Ns group. Compound **7b** was coupled with carboxylic acid **43**, derived from L-serine,^(14c,29) using Ghosez's reagent⁽³⁴⁾ to afford compound **47** in 57% yield. After selective removal of the TBS group by treatment with 10-camphorsulfonic acid (CSA) in MeOH–CH₂Cl₂ (2:3), the Mitsunobu reaction⁽¹⁵⁾ of obtained alcohol **42** using diethyl azodicarboxylate (DEAD) and PPh₃ proceeded smoothly to give 1,4-diazepanone **48** in 92% yield.

Previous studies reported that both the hydroxy group and ester on the 1,4-diazepanone ring were oriented in pseudo-axial positions.^(11u,v,y) In contrast, our DFT calculation suggested that the siloxy group and ester on 1,4-diazepanone **48** were oriented in pseudo-equatorial and pseudo-axial positions, respectively (Figure 4, conformation **X**). Conformation **X** was more stable than conformation **Y**, in which both substituents were oriented in pseudo-axial positions, presumably owing to the presence of a bulky substituent (*p*Ns group) on the nitrogen atom. The coupling constant of 3.3 Hz observed between H_a and H_b did not contradict predicted conformation **X**. Compound **48** was converted to secondary amine **49** in 90% yield by treatment with PhSH and K₂CO₃. As a model study for introducing the side chain, compounds **41a** and **41b** were pre-

pared by introducing methyl and 2,2,2-trichloroethoxycarbonyl (Troc) groups, respectively. In the synthesis of **41a**, an α,β -unsaturated ester **50** was obtained as byproduct owing to the basic workup after treatment with aqueous hydrogen fluoride (HF). Consequently, the isolated yield of **41a** was low.



Scheme 7. Synthesis of 1,4-diazepane **41** using a Mitsunobu reaction.

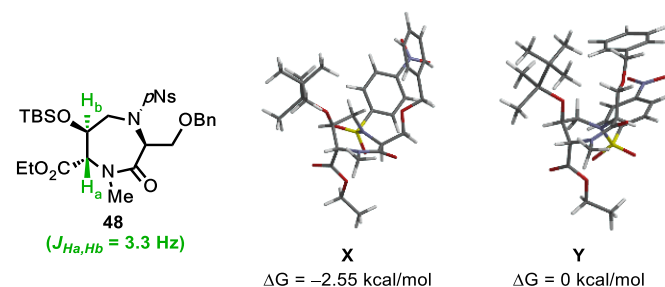
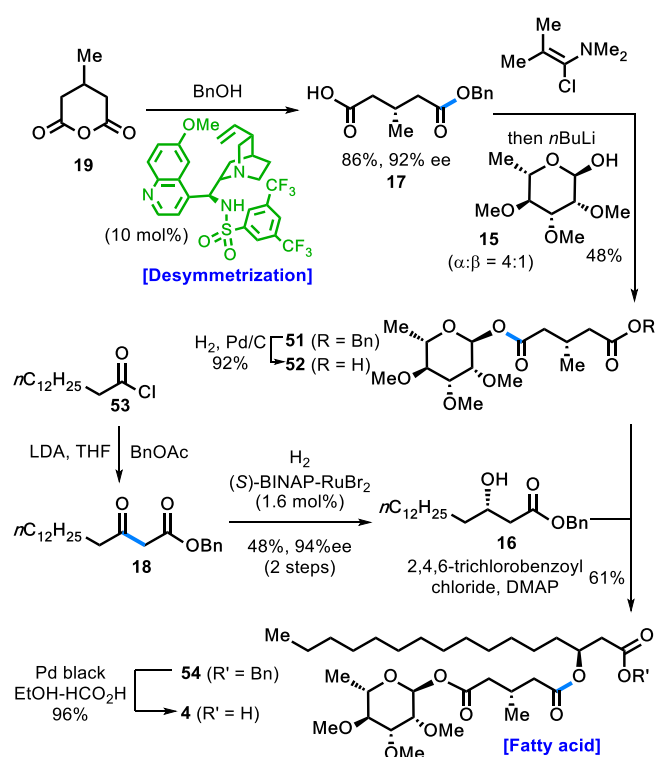


Figure 4. Possible conformations **X** and **Y** of compound **48**, calculated using Gaussian '09 at the B3LYP/6-31G(d) level of theory (DFT).

Next, the synthesis of a fatty acid side chain **4** started with the desymmetrization of 3-methyl glutaric acid anhydride **19** using a cinchona alkaloid catalyst developed by Song and coworkers (Scheme 8).⁽³²⁾ The resulting carboxylic acid **17** (92% ee) was coupled with L-rhamnose derivative **15**⁽³⁰⁾ through acid chloride formation to give ester **51**. After separating a small amount of the undesired diastereomers, a benzyl group was removed by hydrogenolysis in the presence of Pd/C to afford carboxylic acid **52**. β -Hydroxybenzyl ester **16** was synthesized by Noyori asymmetric reduction⁽³¹⁾ of known β -ketoester **18**,⁽³⁵⁾ which was prepared from myristoyl chloride **53**. Ester **16** was condensed with carboxylic acid **52** under Yamaguchi conditions.^(13d) Protected fatty acid side chain **54** was successfully converted into the fatty acid fragment of caprazamycin A (**4**), which had the same stereochemistry as the natural product, in the presence of Pd/C under a hydrogen atmosphere.



Scheme 8. Synthesis of fatty acid side chain **4**.

With fatty acid side chain **4** and model 1,4-diazepanones **41a** and **41b** in hand, our attention turned to introducing the fatty acid side chain onto the 1,4-diazepanone core. Initially, the direct coupling of **4** onto model 1,4-diazepanone **41a** was investigated (Scheme 9). When using EDCI, DCC, or PyBOP, the reaction gave a complex mixture.⁽³⁶⁾ To avoid undesired β -elimination of the β -alkoxyester unit, condensation with 2,4-

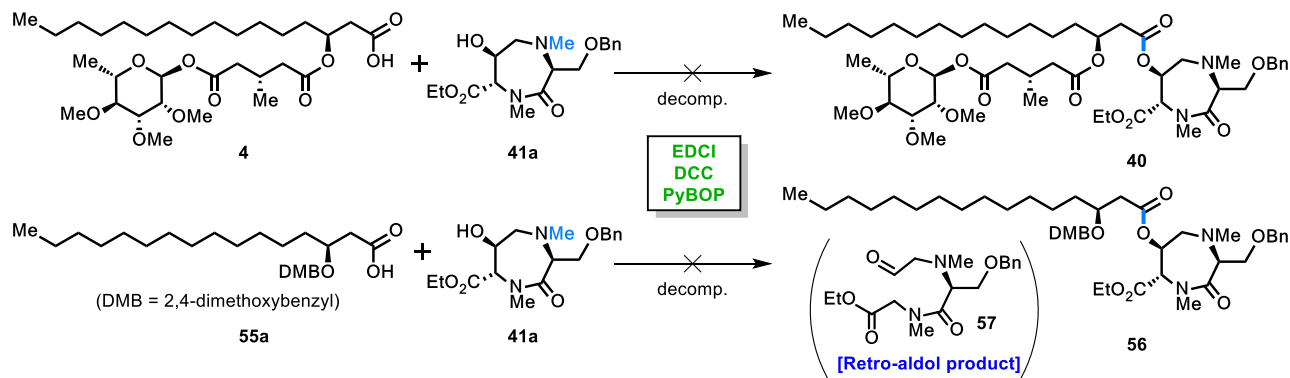
dimethoxybenzyl (DMB)-protected β -hydroxy carboxylic acid **55a** was attempted.⁽³⁷⁾ However, reactions using EDCI, DCC, or PyBOP did not afford desired coupling product **56**, with aldehyde **57** observed as a byproduct produced by a retro-aldol reaction. In contrast, the reaction of Troc-protected 1,4-diazepanone **41b** with DMB-protected β -hydroxy carboxylic acid **55a** using EDCI proceeded smoothly, giving desired coupling product **58a** in excellent yield. For subsequent transformations, including protecting group removal, triethylsilyl (TES)-protected β -hydroxy carboxylic acid **55b** was employed in this condensation reaction, affording desired ester **58b** in 62% yield. These results indicated that compound **41b** was more reactive than **41a** in this transformation, despite having the same conformation. Our DFT calculations suggested that the enhanced reactivity of **41b** might be due to the presence of a hydrogen bond between the hydroxy and Troc groups (Figure 5).

Ester **58b** was treated with zinc and AcOH to reductively remove the Troc group (Scheme 9). The resultant secondary amine was subjected to reductive amination followed by removal of the TES group to furnish *N*-methylated compound **59** in 66% yield. The glutaric monoester unit **52** was then successfully introduced to secondary alcohol **59** under Yamaguchi conditions. This stepwise method for introducing the fatty acid side chain was robust owing to no decomposition of the unstable structure and no epimerization. Therefore, this route would be applicable to introducing the fatty acid side chains of not only caprazamycins, but related liponucleoside antibiotics such as liposidomycins and spharimicins.

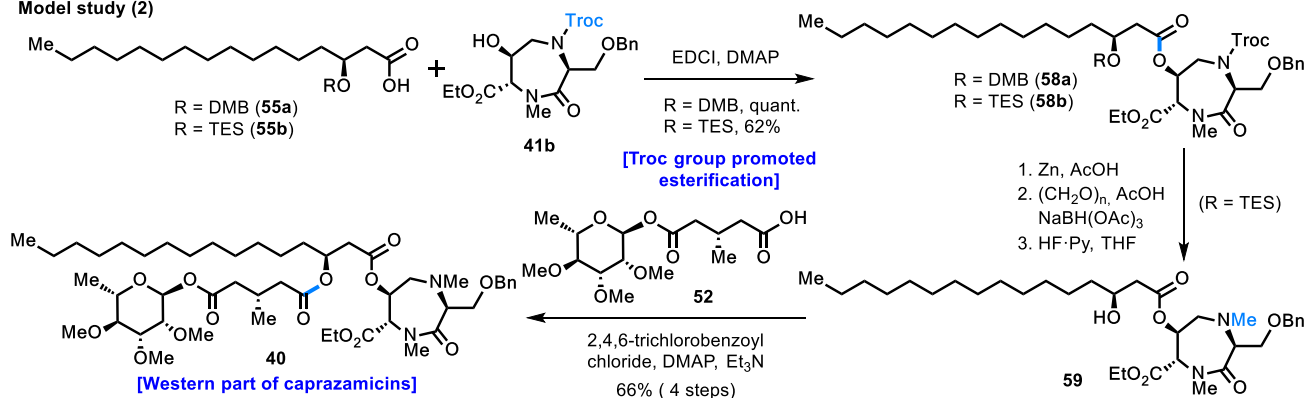
3. Total synthesis of caprazol (**2**) and caprazamycin A (**1**)

With an established route for introducing the fatty acid side chain in hand, we next focused on constructing a 1,4-diazepanone core bearing amino-ribose and uridine moieties and introducing the side chain to achieve a total synthesis of caprazamycin A. Glycosylation of *syn*- β -hydroxyamino acid derivatives **10** with compound **9** proceeded in a β -selective manner under the conditions reported by Matsuda and Ichikawa (Scheme 10).⁽¹²⁾ Reduction of the azide in coupling product **60**, followed by protection of the resulting amine with a Cbz group and methyl ester hydrolysis afforded carboxylic acid **8**. Carboxylic acid **8** was coupled with *anti*- β -hydroxyl acid derivative **7a**, in which the secondary alcohol was protected as a TBS ether, using Ghosez's reagent⁽³⁴⁾ via acid chloride formation. Selective TBS group removal from the primary alcohol of **61a** gave cyclization precursor **6a**. To investigate the Mitsunobu cyclization, compound **6b** was also synthesized from carboxylic acid **8** and *anti*- β -hydroxyl acid derivative **7b** using a similar sequence. No β -elimination or epimerization were observed in these transformations.

Model study (1)



Model study (2)



Scheme 9. Introduction of fatty acid onto diazepanone **41**.

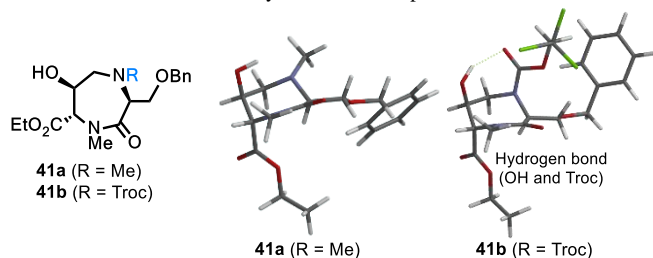
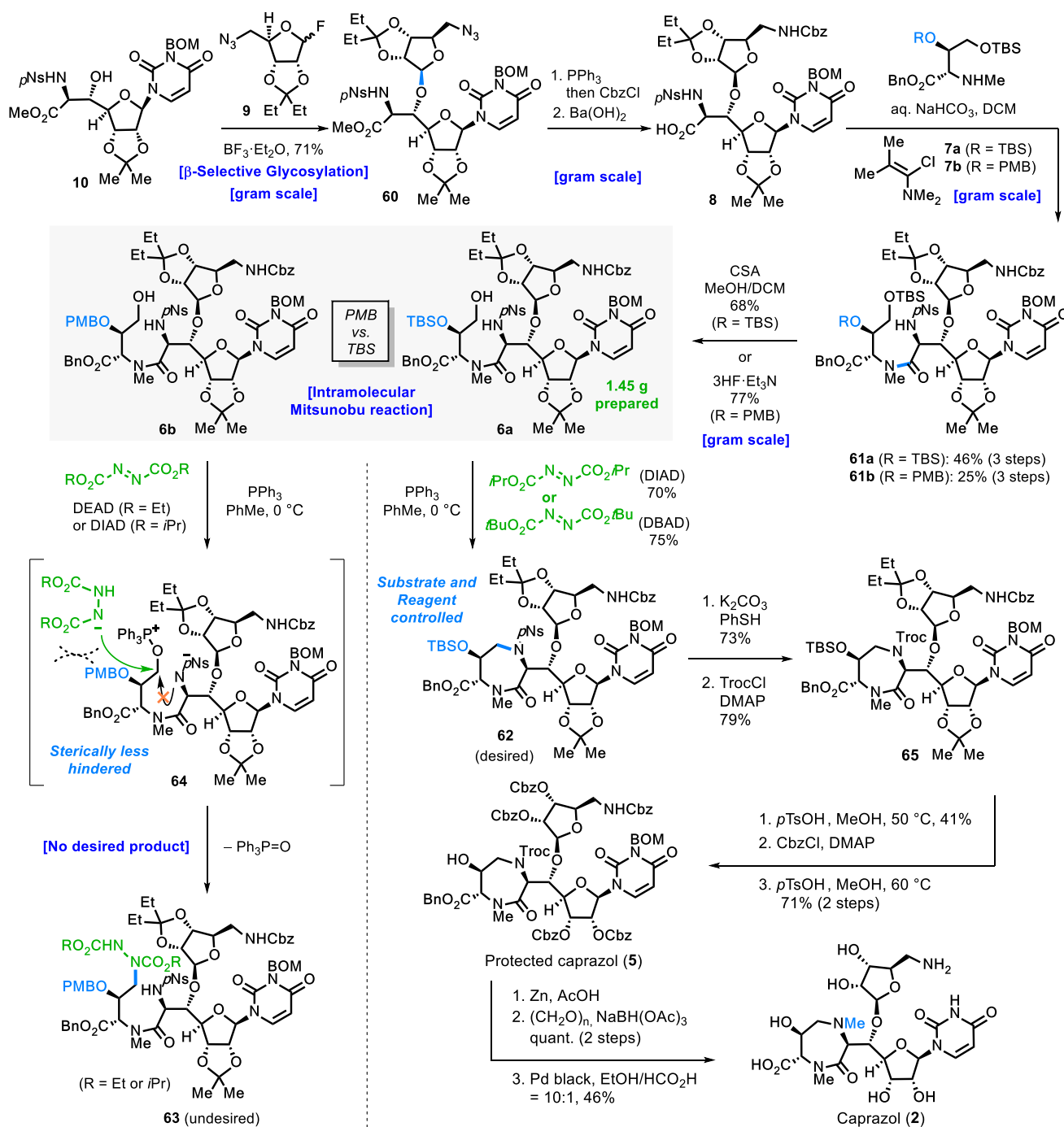


Figure 5. Conformations of compounds **41a** and **41b** calculated by Gaussian '09 at the B3LYP/6-31G(d) level of theory (DFT).

Next, we focused on construction the 1,4-diazepanone skeleton using a Mitsunobu reaction. Initially, the intramolecular Mitsunobu reaction of compound **6b**, bearing a secondary alcohol protected as a *p*-methoxybenzyl (PMB) ether, was attempted. Although the cyclization of simple model compound **42** proceeded smoothly (Scheme 7), the reaction of **6b** did not give desired cyclization product, even when diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) were employed in the presence of PPh₃. Mass spectrometry analysis indicated that byproduct **63** was generated in this reaction through an intermolecular S_N2 reaction with hydrazine-1,2-dicarboxylate produced by the reduction of DEAD

or DIAD. These results indicated that the intermolecular S_N2 reaction of intermediate **64** was preferred over the desired intramolecular S_N2 reaction. To suppress this side reaction, we employed sterically bulkier substrate **6a** bearing a TBS group adjacent to the primary alcohol. As expected, the reaction with DIAD afforded cyclized product **62** in 70% yield. Furthermore, using di-*tert*-butyl azodicarboxylate (DBAD), which is bulkier than DIAD, improved the yield to 75%. By increasing the bulkiness of both the substrate and reagent, the undesired intermolecular S_N2 reaction was suppressed to afford the 1,4-diazepanone product.

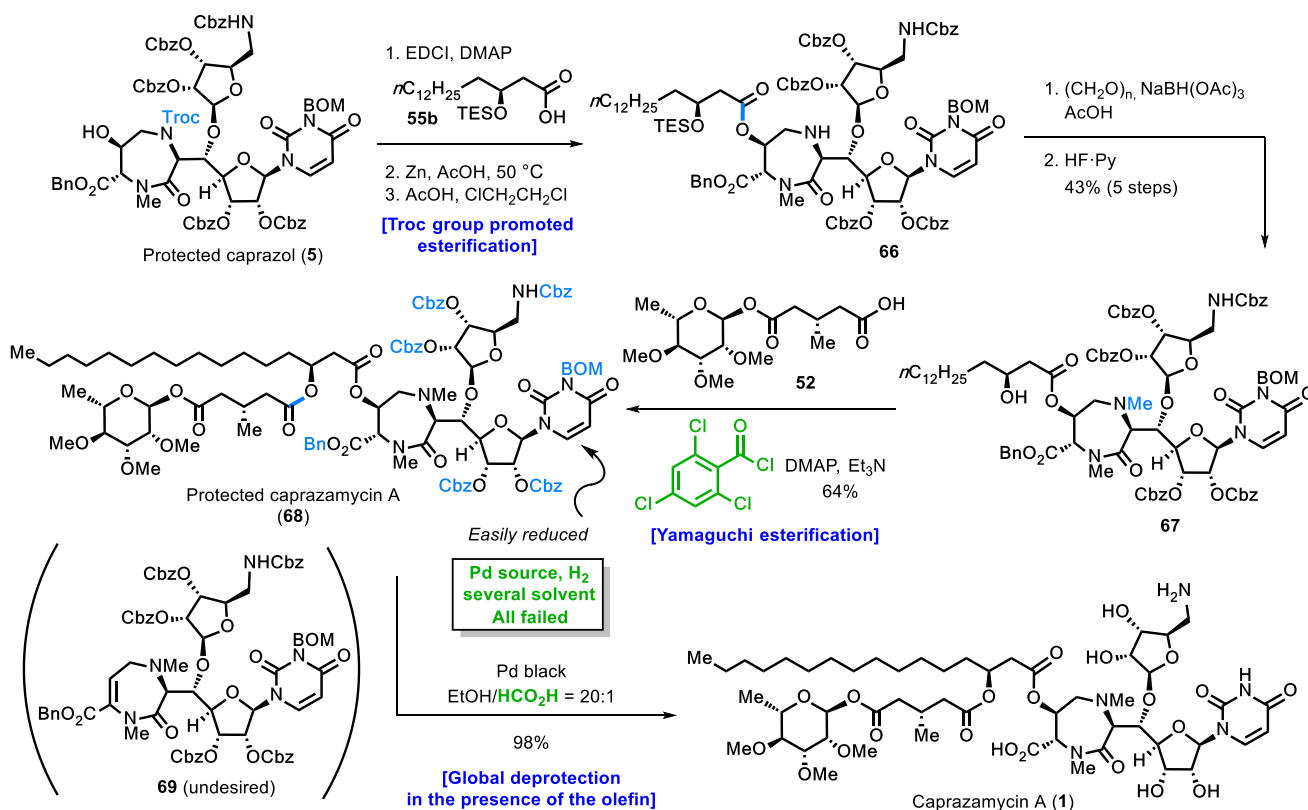
Before introducing the fatty acid side chain, cyclized product **62** was converted into protected caprazol **5** to facilitate the final global deprotection (Scheme 10). After removing the *p*Ns group, a Troc group was introduced to afford compound **65** in 58% yield over two steps. Two acetal groups were carefully hydrolysed under acidic conditions and the obtained tetraol was converted to a Cbz carbonate, followed by treatment under acidic conditions to remove the TBS group. To confirm the stereochemistry of protected caprazol **5**, it was converted to caprazol (**2**). Troc group removal followed by reductive amination gave a tertiary amine, followed by treatment with Pd black in the presence of formic acid to give caprazol (**2**), which had spectra data identical to those reported previously.^(12d,e,13c)



Scheme 10. Investigation of Mitsunobu reaction and synthesis of caprazol (2).

To complete the first total synthesis of caprazamycin A (**1**), we carefully applied model studies to couple protected caprazol **5** with fatty acid side chain **55b** (Scheme 11). Condensation of **5** with **55b** using EDCI successfully proceeded to afford the desired acylated product without undesired side reactions, such as β -elimination, epimerization, and retro-aldol reaction on the 1,4-diazepanone. After removing the Troc

group in the presence of zinc and acetic acid, the resultant carbamic acid intermediate was treated with acetic acid to give compound **66** via decarboxylation. Reductive amination of secondary amine **66** was followed by TES group removal to afford corresponding alcohol **67**. Yamaguchi conditions^(13d) were applied to introduce the fatty acid side chain **52** containing rhamnose. Although the reaction

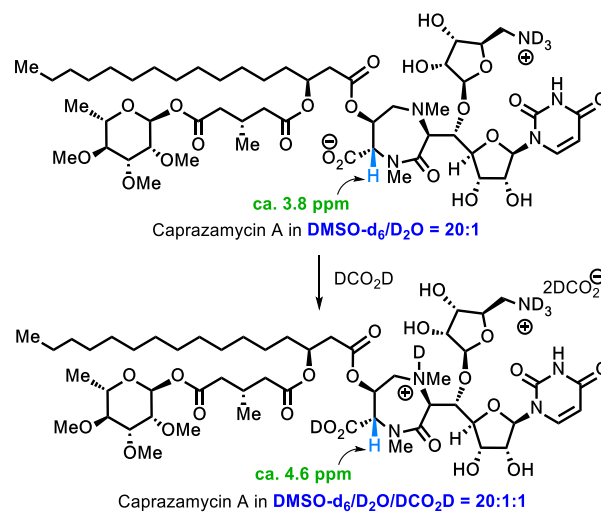


Scheme 11. The first total synthesis of caprazamycin A (**1**).

afforded protected caprazamycin A (**68**), byproduct **69** was readily formed through β -elimination under these conditions. Therefore, the amounts of Et₃N and 4-dimethylaminopyridine (DMAP) were reduced, and the reaction time was shortened. As a result, protected caprazamycin A (**68**) was obtained in 64% yield.

Finally, conditions for the global deprotection of five Cbz, one BOM, and one Bn groups in the protected caprazamycin **A** (**68**) while avoiding reduction of the uracil olefin were investigated. Using 10% Pd/C under a hydrogen atmosphere removed the protecting groups, but also resulted in olefin hydrogenation. Although various palladium (Pd) catalysts, including 5% Pd/C, Pd/C(en), and Pd(OH)₂/C, in the presence of various hydrogen sources (H₂, cyclohexadiene, and formic acid) were examined, none were able to suppress olefin reduction. In contrast, treatment with EtOH/formic acid (20:1, v/v) in the presence of Pd black resulted in a near-quantitative clean deprotection without olefin reduction. After careful neutralization, the spectral data, including NMR (DMSO-*d*₆/D₂O, 20:1) and HRMS data, of the synthetic sample were identical to those of the natural product.⁽¹⁾ Therefore, the first total synthesis of caprazamycin **A** (**1**) was successfully accomplished. The NMR spectra of caprazamycin **A** (**1**) were concentration- and pK_a-dependent (Scheme 12). When NMR spectra of **1**

were measured using DMSO- d_6 /D $_2$ O/DCO $_2$ D (20:1:1), the carboxylic acid α -proton in **1** was shifted downfield compared with that measured in



Scheme 12. ^1H NMR spectrum of caprazamycin A (**1**).

DMSO- d_6 /D $_2$ O (20:1). This indicated that caprazamycin A was in zwitterion form in DMSO- d_6 /D $_2$ O, but had a protonated carboxylic acid in the presence of formic acid.

Conclusions

We have developed a diastereoselective aldol reaction of diethyl isocyanomalonate **13** and phenylcarbamate **21** for the synthesis of β -hydroxy amino acid derivatives. Thiourea catalyst **14** effectively obtained the desired 5'S-isomer **11a** in the aldol reaction of aldehyde **12** bearing an isopropylidene acetal moiety. The resultant aldol products were readily converted into *syn*- β -hydroxy amino acid derivatives **10**, **38**, and **39** bearing several protecting groups. The 1,4-diazepanone core structure of caprazamycin A was obtained using a Mitsunobu reaction. A synthetic route for introducing a fatty acid side chain was established using a stepwise sequence. Finally, we achieved the first total synthesis of caprazamycin A by identifying conditions for global deprotection without hydrogenation of the olefin in the uridine unit. These results and the established synthetic route will guide the synthesis of related liponucleoside antibiotics bearing fatty acid side chains, including liposidomycins and spaerimicin A, and investigations into the synthesis of a related natural product are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data (^1H and ^{13}C NMR, MS) for all new compounds as well as summaries of unsuccessful approaches. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) a) Igarashi, M.; Nakagawa, N.; Doi, S.; Hattori, N.; Naganawa, H.; Hamada, M. Caprazamycin B, a Novel Antituberculosis Antibiotic, from *Streptomyces* sp. *J. Antibiot.* **2003**, *56*, 580; b) Takeuchi, T.; Igarashi, M.; Naganawa, H. Caprazamycins D, G, D1, G1, Antibiotics, and their preparation method. JP P2003-12687A, **2003**; c) Igarashi, M.; Takahashi, Y.; Shitara, T.; Nakamura, H.; Naganawa, H.; Miyake, T.; Akamatsu, Y. Caprazamycins, Novel Liponucleoside Antibiotics, from *Streptomyces* sp. *J. Antibiot.* **2005**, *58*, 327.

- (2) a) Isono, K.; Uramoto, M.; Kusakabe, H.; Kimura, K.; Izaki, K.; Nelson, C. C.; McCloskey, J. A. Liposidomycins: Novel Nucleoside Antibiotics Which Inhibit Bacterial Peptidoglycan Synthesis. *J. Antibiot.* **1985**, *38*, 1617; b) Kimura, K.; Ikeda, Y.; Kagami, S.; Yoshihama, M.; Suzuki, K.; Osada, H.; Isono, K. Selective Inhibition of the Bacterial Peptidoglycan Biosynthesis by the New Types of Liposidomycins. *J. Antibiot.* **1998**, *51*, 1099; c) Ubukata, M.; Kimura, K.; Isono, K.; Nelson, C. C.; Gregson, J. M.; McCloskey, J. A. Structure elucidation of liposidomycins, a class of complex lipid nucleoside antibiotics. *J. Org. Chem.* **1992**, *57*, 6392; d) Kimura, K.; Ikeda, Y.; Kagami, S.; Yoshihama, M.; Ubukata, M.; Esumi, Y.; Osada, H.; Isono, K. New Types of Liposidomycins that Inhibit Bacterial Peptidoglycan Synthesis and are Produced by *Streptomyces*. *J. Antibiot.* **1998**, *51*, 647; e) Kimura, K.; Kagami, S.; Ikeda, Y.; Takahashi, H.; Yoshihama, M.; Kusakabe, H.; Osada, H.; Isono, K. New Types of Liposidomycins that Inhibit Bacterial Peptidoglycan Synthesis and are Produced by *Streptomyces*. *J. Antibiot.* **1998**, *51*, 640.
- (3) McDonald, L. A.; Barbieri, L. R.; Carter, G. T.; Lenoy, E.; Lotvin, J.; Petersen, P. J.; Siegel, M. M.; Singh, G.; Williamson, R. T. Structures of the Muraymycins, Novel Peptidoglycan Biosynthesis Inhibitors. *J. Am. Chem. Soc.* **2002**, *124*, 10260.
- (4) Fujita, Y.; Kizuka, M.; Funabashi, M.; Ogawa, Y.; Ishikawa, T.; Nonaka, K.; Takatsu, T. A-90289 A and B, new inhibitors of bacterial translocase I, produced by *Streptomyces* sp. SANK 60405. *J. Antibiot.* **2011**, *64*, 495.
- (5) Funabashi, M.; Baba, S.; Takatsu, T.; Kizuka, M.; Ohata, Y.; Tanaka, M.; Nonaka, K.; Ducho, A. P. C.; Chen, W.-C. L.; Van Lanen, S. G. Structure-based gene targeting discovery of spaerimicin, a bacterial translocase I inhibitor. *Angew. Chem. Int. Ed.* **2013**, *52*, 11607.
- (6) a) Kimura, K.; Bugg, T. D. H. Recent advances in antimicrobial nucleoside antibiotics targeting cell wall biosynthesis. *Nat. Prod. Rep.* **2003**, *20*, 252; b) Dini, C.; Collette, P.; Drochon, N.; Guillot, J. C.; Lemoine, G.; Mauvais, P.; Aszodi, J. Synthesis of the nucleoside moiety of liposidomycins: elucidation of the pharmacophore of this family of MraY inhibitors. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1839.
- (7) Kaysser, L.; Lutsch, L.; Siebenberg, S.; Wemakor, E.; Kammerer, B.; Gust, B. Identification and Manipulation of the Caprazamycin Gene Cluster Lead to New Simplified Liponucleoside Antibiotics and Give Insights into the Biosynthetic Pathway. *J. Biol. Chem.* **2009**, *284*, 14987.
- (8) Barnard-Britson, S.; Chi, X.; Nonaka, K.; Spork, A. P.; Tibrewal, N.; Goswami, A.; Pahari, P.; Ducho, C.; Rohr, J.; Van Lanen, S. G. Amalgamation of Nucleosides and Amino Acids in Antibiotic Biosynthesis: Discovery of an L-Threonine:Uridine-5'-Aldehyde Transaldolase. *J. Am. Chem. Soc.* **2012**, *134*, 18514.
- (9) a) Ishizaki, Y.; Hayashi, C.; Inoue, K.; Igarashi, M.; Takahashi, Y.; Pujari, V.; Crick, D. C.; Brennan, P. J.; Nomoto, A. Inhibition of the First Step in Synthesis of the Mycobacterial Cell Wall Core, Catalyzed by the GlcNAc-1-phosphate Transferase WecA, by the Novel Caprazamycin Derivative CPZEN-45. *J. Biol. Chem.* **2013**, *288*, 30309; b) Takahashi, Y.; Igarashi, M.; Miyake, T.; Soutome, H.; Ishikawa, K.; Komatsuki, Y.; Koyama, Y.; Nakagawa, N.; Hattori, S.; Inoue, K.; Doi, N.; Akamatsu, Y. Novel semisynthetic antibiotics from caprazamycins A-G: caprazene derivatives and their antibacterial activity. *J. Antibiot.* **2013**, *66*, 171.
- (10) For review, see: Watanabe, T. Synthesis of Caprazamycins and Related Natural Products. *Heterocycles*, **2017**, *95*, 662.

- (11) a) Wlegmann, D.; Spork, A. P.; Niro, G.; Ducho, C. Where Are They Now? -Ribosylation of an Acid-Labile Glycosyl Acceptor as a Potential Key Step for the Synthesis of Nucleoside Antibiotics. *Synlett*, **2018**, 29, 440; b) Nakajima, N.; Seida, T.; Furuno, A.; Asahi, T.; Kishimoto, T.; Hamada, M. Synthetic Studies of Liposidomycin Degradation Product: Model Studies of Diazepanone Ring Construction. *Heterocycles*, **2017**, 95, 1074; c) Mitachi, K.; Aleiwei, B. A.; Schneider, C. M.; Siricilla, S.; Kurosu, M. Stereocontrolled Total Synthesis of Muraymycin D1 Having a Dual Mode of Action against Mycobacterium tuberculosis. *J. Am. Chem. Soc.* **2016**, 138, 12975; d) Fer, M. J.; Bouhss, A.; Patrão, M.; Corre, L. L.; Pietrancosta, N.; Amoroso, A.; Joris, B.; Mengin-Lecreulx, D.; Calvet-Vitale, S.; Gravier-Pelletier, C. 5'-Methylene-triazole-substituted-aminoribosyl uridines as MraY inhibitors: synthesis, biological evaluation and molecular modeling. *Org. Biomol. Chem.* **2015**, 13, 7193; e) Ichikawa, S.; Yamaguchi, M.; Hsuan, L. S.; Kato, Y.; Matsuda, A. Carbaprazamycins: Chemically Stable Analogues of the Caprazamycin Nucleoside Antibiotics. *ACS Infect. Dis.* **2015**, 1, 151; f) Spork, A. P.; Büschleb, M.; Ries, O.; Wiegmann, D.; Boettcher, S.; Mihalyi, A.; Bugg, T. D. H.; Ducho, C. Lead Structures for New Antibacterials: Stereocontrolled Synthesis of a Bioactive Muraymycin Analogue. *Chem. Eur. J.* **2014**, 20, 15292; g) Fer, M. J.; Doan, P.; Prangé, T.; Calvet-Vitale, S.; Gravier-Pelletier, C. A Diastereoselective Synthesis of 5'-Substituted-Uridine Derivatives. *J. Org. Chem.* **2014**, 79, 7758; h) Miyaoka, H.; Wada, J.; Kawashima, E. Synthesis of the Diazepanone-Nucleoside Core Structure of Liposidomycins and Caprazamycins Based on 7-Exo Cyclization of Epoxyamine. *Heterocycles* **2014**, 88, 719; i) Sarabia, F.; Vivar-García, C.; García-Ruiz, C.; Martín-Ortiz, L.; Romero-Carrasco, A. Exploring the Chemistry of Epoxy Amides for the Synthesis of the 2"-epi-Diazepanone Core of Liposidomycins and Caprazamycins. *J. Org. Chem.* **2012**, 77, 1328; j) Ii, K.; Ichikawa, S.; Al-Dabbagh, B.; Bouhss, A.; Matsuda, A. Function-Oriented Synthesis of Simplified Caprazamycins: Discovery of Oxazolidine-Containing Uridine Derivatives as Antibacterial Agents against Drug-Resistant Bacteria. *J. Med. Chem.* **2010**, 53, 3793; k) Spork, A. P.; Koppermann, S.; Dittich, B.; Herbst-Irmer, R.; Ducho, C. Efficient synthesis of the core structure of muraymycin and caprazamycin nucleoside antibiotics based on a stereochemically revised sulfur ylide reaction. *Tetrahedron: Asymmetry* **2010**, 21, 763; l) Monasson, O.; Ginisty, M.; Mravljak, J.; Bertho, G.; Gravier-Pelletier, C.; Merrer, Y. L. Synthetic studies towards diazepanone scaffolds. *Tetrahedron: Asymmetry* **2009**, 20, 2320; m) Xu, X.; Trunkfield, H. A. E.; Bugg, T. D. H.; Qing, F. L. Synthesis of gem-difluorinated nucleoside analogues of the liposidomycins and evaluation as MraY inhibitors. *Org. Biomol. Chem.* **2008**, 6, 157; n) Monasson, O.; Ginisty, M.; Bertho, G.; Gravier-Pelletier, C.; Merrer, Y. L. Efficient synthesis of polyfunctionalised enantiopure diazepanone scaffolds. *Tetrahedron Lett.* **2007**, 48, 8149; o) Fukunishi, S.; Ubukata, M.; Nakajima, N. Synthetic Studies of Liposidomycin Degradation Product: Model Studies of Uracil Group Introduction. *Heterocycles* **2007**, 73, 627; p) Sarabia, F.; Martín-Ortiz, L.; Lopez-Herrera, F. J. A Convergent Synthetic Approach to the Nucleoside-Type Liposidomycin Antibiotics. *Org. Lett.* **2003**, 5, 3927; q) Yamashita, A.; Norton, E. B.; Williamson, R. T.; Ho, D. M.; Sinishtaj, S.; Mansour, T. S. Use of Bis-(chiral α -methylbenzyl)glycine Esters for Synthesis of Enantiopure β -Hydroxyamino Esters. *Org. Lett.* **2003**, 5, 3305; r) Drouillard, B.; Poupardin, O.; Bourdreux, Y.; Greck, C. Diastereoselective syntheses of α -amino- β -hydroxyesters precursors of the ribosyl-diazepanone core of the liposidomycins. *Tetrahedron Lett.* **2003**, 31, 2781; s) Knapp, S.; Morriello, G. J.; Doss, G. A. Synthesis of the Liposidomycin Diazepanone Nucleoside. *Org. Lett.* **2002**, 4, 603; t) Gravier-Pelletier, C.; Milla, M.; Merrer, Y. L.; Depeyay, J. C. Liposidomycins – Synthetic Studies Towards the Ribosyldiazepanone Moiety. *Eur. J. Org. Chem.* **2001**, 2001, 3089; u) Knapp, S.; Morriello, G. J.; Nandan, S. R.; Emge, T. J.; Doss, G. A.; Mosley, R. T.; Chen, L. Assignment of the Liposidomycin Diazepanone Stereochemistry. *J. Org. Chem.* **2001**, 66, 5822; v) Kim, K. S.; Ahn, Y. H. Synthesis of the diazepanone-nucleoside portion of liposidomycins by aldol reaction of the enolate of diazepanone with a nucleoside 5'-aldehyde. *Tetrahedron: Asymmetry* **1998**, 9, 3601; w) Merrer, Y. L.; Gravier-Pelletier, C.; Gerrouache, M.; Depeyay, J. C. Access to enantiopure ribosyl-diazepanone core of liposidomycins. *Tetrahedron Lett.* **1998**, 39, 385; x) Kim, K. S.; Cho, I. H.; Ahn, Y. H.; Park, J. I. Synthesis of the 1,4-diazepan-2-one moiety of liposidomycins. *J. Chem. Soc. Perkin Trans. 1* **1995**, (0), 1783; y) Knapp, S.; Nandan, S.; Resnick, L. Synthesis of the liposidomycin diazepanone. *Tetrahedron Lett.* **1992**, 33, 5485.
- (12) a) Ichikawa, S. Function-Oriented Synthesis: How to Design Simplified Analogues of Antibacterial Nucleoside Natural Products? *Chem. Rec.* **2016**, 16, 1106; b) Ichikawa, S. Fine Synthetic Nucleoside Chemistry Based on Nucleoside Natural Products Synthesis. *Chem. Pharm. Bull.* **2008**, 56, 1059. c) Hirano, S.; Ichikawa, S.; Matsuda, A. Synthesis of Caprazamycin Analogues and Their Structure-Activity Relationship for Antibacterial Activity. *J. Org. Chem.* **2008**, 73, 569; d) Hirano, S.; Ichikawa, S.; Matsuda, A. Development of a Highly β -Selective Ribosylation Reaction without Using Neighboring Group Participation: Total Synthesis of (+)-Caprazol, a Core Structure of Caprazamycins. *J. Org. Chem.* **2007**, 72, 9936; e) Hirano, S.; Ichikawa, S.; Matsuda, A. Total Synthesis of Caprazol, a Core Structure of the Caprazamycin Antituberculosis Antibiotics. *Angew. Chem. Int. Ed.* **2005**, 44, 1854.
- (13) a) Takeuchi, T.; Abe, H.; Watanabe, T.; Shibasaki, M. Catalytic asymmetric synthesis of CPZEN-45. *Tetrahedron Lett.* **2016**, 57, 2901; b) Abe, H.; Gopinath, P.; Ravi, G.; Wang, L.; Watanabe, T.; Shibasaki, M. Synthesis of caprazamycin B. *Tetrahedron Lett.* **2015**, 56, 3782; c) Gopinath, P.; Wang, L.; Abe, H.; Ravi, G.; Masuda, T.; Watanabe, T.; Shibasaki, M. Catalytic Asymmetric Total Synthesis of (+)-Caprazol. *Org. Lett.* **2014**, 16, 3364; d) Gopinath, P.; Watanabe, T.; Shibasaki, M. Studies on Catalytic Enantioselective Total Synthesis of Caprazamycin B: Construction of the Western Zone. *J. Org. Chem.* **2012**, 77, 9260; e) Gopinath, P.; Watanabe, T.; Shibasaki, M. Catalytic Enantioselective Desymmetrization of meso-Glutaric Anhydrides Using a Stable Ni₂-Schiff Base Catalyst. *Org. Lett.* **2012**, 14, 1358.
- (14) a) Nakamura, H.; Yoshida, T.; Tsukano, C.; Takemoto, Y. Synthesis of CPZEN-45: Construction of the 1,4-Diazepin-2-one Core by the Cu-Catalyzed Intramolecular Amidation of a Vinyl Iodide. *Org. Lett.* **2016**, 18, 2300; b) Nakamura, H.; Tsukano, C.; Yasui, M.; Takemoto, Y. Total Synthesis of (-)-Caprazamycin A. *Angew. Chem. Int. Ed.* **2015**, 54, 3136; c) Tsukano, C.; Yokouchi, S.; Girard, A. L.; Kuribayashi, T.; Sakamoto, S.; Enomoto, T.; Takemoto, Y. Platinum catalyzed 7-endo cyclization of internal alkynyl amides and its application to synthesis of the caprazamycin core. *Org. Biomol. Chem.* **2012**, 10, 6074; d) Girard, A. L.; Enomoto, T.; Yokouchi, S.; Tsukano, C.; Takemoto, Y. Control of 6-Exo and 7-Endo Cyclizations of Alkynylamides using Platinum and Bismuth Catalysts. *Chem. Asian J.* **2011**, 6, 1321.
- (15) Kan, T.; Fukuyama, T. New strategies: a highly versatile synthetic method for amines. *Chem. Commun.* **2004**, (0), 353.
- (16) Sakamoto, S.; Kazumi, N.; Kobayashi, Y.; Tsukano, C.; Takemoto, Y. Asymmetric Synthesis of Trisubstituted Oxa-

- zolidinones by the Thiourea-Catalyzed Aldol Reaction of 2-Isocyanatomalonate Diester. *Org. Lett.* **2014**, *16*, 4758.
- (17) For recent reviews of thiourea-based catalysts, see: a) Connon, S. J. Organocatalysis Mediated by (Thio)urea Derivatives. *Chem. Eur. J.* **2006**, *12*, 5418; b) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107*, 5713; c) Connon, S. J. Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts. *Chem. Commun.* **2008**, (0), 2499; d) Zhang, Z.; Schreiner, P. R. (Thio)urea organocatalysis—What can be learnt from anion recognition? *Chem. Soc. Rev.* **2009**, *38*, 1187; e) Takemoto, Y. Development of Chiral Thiourea Catalysts and Its Application to Asymmetric Catalytic Reactions. *Chem. Pharm. Bull.* **2010**, *58*, 593. (f) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. Design Strategies for Enhanced Hydrogen - Bond Donor Catalysts. *Eur. J. Org. Chem.* **2014**, *2014*, 2633.
 - (18) Part of this work has been published in preliminary communications, see refs. 14a and 14b.
 - (19) a) Cesa, M. C.; Rinz, J. E.; Kopp, T. T. Aryl oxime derivatives of hydantoins. U.S. patent, **1987**, US 4705864 A; b) Cesa, M. C.; Rinz, J. E.; Klopman, G.; Kopp, T. T. N,N'-disubstituted ureas. U.S. patent, **1988**, US 4740611 A.
 - (20) Wang, R.; Steensma, D. H.; Takaoka, Y.; Yun, J. W.; Kajimoto, T.; Wong, C.-H. A search for pyrophosphate mimics for the development of substrates and inhibitors of glycosyltransferases. *Bioorg. Med. Chem.* **1997**, *5*, 661.
 - (21) a) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. On the communication of chirality from furanose and pyranose rings to monosaccharide side chains: anomalous results in the glucose series. *Tetrahedron* **1986**, *42*, 2809; b) Danishefsky, S. J.; DeNinno, S. L.; Chen, S.-H.; Boisvert, L.; Barbachyn, M. Fully synthetic stereoselective routes to the differentially protected subunits of the tunicamycins. *J. Am. Chem. Soc.* **1989**, *111*, 5810; c) Chen, X.; Wiemer, D. F. α -Phosphono Lactone Analogues of Cytidine and Cytosine Arabinoside Diphosphates: Synthesis via Ring Closing Metathesis. *J. Org. Chem.* **2003**, *68*, 6597.
 - (22) Ichikawa and coworkers recently reported controlling diastereoselectivity in the Mukaiyama aldol reaction of compound **12** using Lewis acids, see Yamamoto, K.; Yakushiji, F.; Matsumura, T.; Ichikawa, S. Total Synthesis of Tunicamycin V. *Org. Lett.* **2018**, *20*, 256.
 - (23) The transition states were also calculated with several different functionals, including dispersion correction. See the Supporting Information for the details of computational studies.
 - (24) Compound **25** was prepared by IBX oxidation of a known BOM-protected uridine, see: Silva, D. J.; Sofia, M. J. Novel carbohydrate scaffolds. Assembly of a uridine-mannose scaffold based on tunicamycin. *Tetrahedron Lett.* **2000**, *41*, 855.
 - (25) Compound **26** was prepared from uridine in five steps: (i) TBS protection of the 5'-hydroxy group; (ii) BOM protection of the nitrogen atom; (iii) TIPS protection of the 2',3'-hydroxy groups; (iv) selective removal of the TBS group; and (v) Dess-Martin oxidation. Also see the supporting information.
 - (26) Spork, A. P.; Wiegmann, D.; Granitzka, M.; Stalke, D.; DUCHO, C. Stereoselective Synthesis of Uridine-Derived Nucleosyl Amino Acids. *J. Org. Chem.* **2011**, *76*, 10083.
 - (27) For the nucleophilic addition of phosphite to aldehyde **27**, Wiemer and coworkers proposed a chelated transition state, in which an attractive electrostatic interaction between silicon and the carbonyl oxygen was postulated; see: Chen, X.; Wiemer, A. J.; Hohl, R. J.; Wiemer, D. F. Stereoselective Synthesis of the 5'-Hydroxy-5'-phosphonate Derivatives of Cytidine and Cytosine Arabinoside. *J. Org. Chem.* **2002**, *67*, 9331.
 - (28) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. Enzyme-Like Chemoselective Acylation of Alcohols in the Presence of Amines Catalyzed by a Tetranuclear Zinc Cluster. *J. Am. Chem. Soc.* **2008**, *130*, 2944.
 - (29) Roberts, T. C.; Smith, P. A.; Cirz, R. T.; Romesberg, F. E. Structural and Initial Biological Analysis of Synthetic Arylomycin A2. *J. Am. Chem. Soc.* **2007**, *129*, 15830.
 - (30) a) Arias-Pérez, M. S.; López, M. S.; Santos, M. J. Imidazole-promoted 1,4-migration of the *tert*-butyldiphenylsilyl group: influence on the selectivity control of the silylation reactions of carbohydrate OH groups. *J. Chem. Soc., Perkin Trans. II*, **2002**, (0), 1549; b) Evans, D. A.; Black, W. C. Total synthesis of (+)-A83543A [(+)-lepidicin A]. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
 - (31) a) Noyori, R.; Takaya, H. BINAP: an efficient chiral element for asymmetric catalysis. *Acc. Chem. Res.* **1990**, *23*, 345; b) Ratovelomanana-Vidal, V.; Girard, C.; Touati, R.; Tranchier, J. P.; Ben Hassine, B.; Genêt, J. P. Enantioselective Hydrogenation of β -Keto Esters using Chiral Diphosphine - Ruthenium Complexes: Optimization for Academic and Industrial Purposes and Synthetic Applications. *Adv. Synth. Catal.* **2003**, *345*, 261.
 - (32) a) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. A highly reactive and enantioselective bifunctional organocatalyst for the methanolytic desymmetrization of cyclic anhydrides: prevention of catalyst aggregation. *Angew. Chem. Int. Ed.* **2008**, *47*, 7872; b) Honjo, T.; Tsumura, T.; Sano, S.; Nagao, Y.; Yamaguchi, K.; Sei, Y. A Chiral Bifunctional Sulfonamide as an Organocatalyst: Alcoholysis of σ -Symmetric Cyclic Dicarboxylic Anhydrides. *Synlett*, **2009**, *20*, 3279.
 - (33) a) Mori, K.; Iwasawa, H. Stereoselective synthesis of optically active forms of δ -multistriatin, the attractant for european populations of the smaller european elm bark beetle. *Tetrahedron*, **1980**, *36*, 87; b) Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torii, S. A facile cleavage of oxirane with hydrazoic acid in dmf A new route to chiral β -hydroxy- α -amino acids. *Tetrahedron Lett.* **1985**, *26*, 5309.
 - (34) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. Synthesis of acyl halides under very mild conditions. *J. Chem. Soc., Chem. Commun.* **1979**, (0), 1180.
 - (35) Taber, D. F.; Dekker, P. B.; Fales, H. M.; Jones, T. H.; Lloyd, H. A. Enantioselective construction of heterocycles. Synthesis of (R,R)-solenopsin B. *J. Org. Chem.* **1988**, *53*, 2968.
 - (36) Since our total synthesis of caprazamycin A, Shibasaki, Watanabe, and coworkers succeeded in directly introducing the fatty acid side chain using 2-methyl-6-nitrobenzoic anhydride (MNBA) for the total synthesis of caprazamycin B, see: ref. 13b.
 - (37) There are a few reports of the introduction of a simple acyl group into the 1,4-diazepanone ring, see: a) Hirano, S.; Ichikawa, S.; Matsuda, A. Structure-activity relationship of truncated analogs of caprazamycins as potential anti-tuberculosis agents. *Bioorg. Med. Chem.* **2008**, *16*, 5123; b) Mravljak, J.; Monasson, O.; Al-Dabbagh, B.; Crouvoisire, M.; Bouhss, A.; Gravier-Pelletier, C.; Merrer, Y. L. Synthesis and biological evaluation of a diazepanone-based library of liposidomycins analogs as MraY inhibitors. *Eur. J. Med. Chem.* **2011**, *46*, 1582; c) also see refs. 11i and 12c.

Table of Contents (TOC)

